LISTING CRITERIA FOR HEART TRANSPLANTATION IN THE NETHERLANDS

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INTRODUCTION

In 2008 a committee under the supervision of both the Netherlands Society of Cardiology and the Netherlands Association for Cardiothoracic surgery (NVVC and NVT) published the first Guidelines for heart transplantation (HTx) in the Netherlands Heart Journal [1].

Here we present updated listing criteria for heart transplantation, on behalf of the three centers involved in heart transplantation in the Netherlands, the Erasmus MC Rotterdam, University Medical Center Groningen and the University Medical Center Utrecht.

These new Dutch listing criteria follow mainly the updated guidelines by the International Society for Heart and Lung Transplantation (ISHLT), and are adapted to the local situation where necessary [2].

PRESENT SITUATION

The situation with regard to the number of heart transplantations in the Netherlands has not improved since 2008. On the contrary, the discrepancy between patients on the waiting list for heart transplantation and the number of donor hearts available, increased even more, resulting in increasingly longer waiting times.

Fig 1A shows the annual number of heart transplantations worldwide, according to the ISHLT [3] and Fig 1B shows the total number in the Netherlands. From these figures it is evident that the number of heart transplantations in Europe is more or less stable, and especially low in the Netherlands. However, the incidence and prevalence of heart failure, in general, increases, leading to more patients with advanced heart failure, potentially qualifying for heart transplantation. Generally in recent years the three transplant centers together perform 40-50 heart transplants/year, while there are ± 120 patients on the waiting list, meaning that the mean waiting time is already approaching three years. It also has to be realized that the limited number of heart transplantations in Europe and especially in the Netherlands can only be performed by using older donor hearts as can be seen from Fig 2 [3]. In the USA, median donor age is still around 28 years, whereas in the Netherlands this is 47 years, with extremes to 67 years; a very important and significant difference. This increase in donor age is mainly due to a shift in the cause of death of the donors, from younger trauma victims to elderly patients dying from cerebrovascular disease. Therefore, Dutch donors in general suffer from more pre-existing cardiovascular disease than donors in the USA. This will affect outcome after heart transplantation, as donor age is not only a continuous risk factor for the incidence of early graft failure after transplantation, potentially leading to the death of the recipient, but it also results in more coronary artery disease late after transplantation (cardiac allograft vasculopathy). [4]

Survival after heart transplantation is good as can be seen in figure 3 as reported by the ISHLT [3], especially considering the poor prognosis of patients with end-stage heart failure without heart transplantation.

Given the scarcity of suitable donor hearts, there is presently no room for substantial broadening of the indications for heart transplantation. This would only result in an even bigger discrepancy between the number of patients on the waiting list and the number of heart transplantations performed, with accompanying further increase in waiting time. Therefore, careful selection of potential candidates for heart transplantation is still mandatory.

Because of the long waiting time, even for urgent recipients with acute progressive heart failure, the use of mechanical circulatory support (MCS) with left ventricular assist devices (LVAD) as bridge to heart transplantation is growing substantially. Presently, according to the ISHLT registry, already 50 % of heart transplants are performed using a LVAD as bridge to transplant [3].

MCS is getting more and more important in the treatment of advanced heart failure and the mid-term outcome with regard to survival and functional recovery is approaching that of heart transplantation [5-8], although it is a very laborious and expensive therapy [9,10]. In the near future MCS will be more and more used as an alternative to transplantation and this certainly will have a huge impact on the selection of transplant candidates.

CRITERIA FOR ACCEPTATION ON THE TRANSPLANT WAITING LIST

"End-stage heart disease not remediable by more conservative measures"

In the light of the foregoing, selection of those patients who may expect to have the greatest benefit in terms of both life expectancy and quality of life from a scarce societal resource is inevitable. Patients who should be considered for heart transplantation are mainly those with severe symptoms of heart failure, and rarely with intractable angina or malignant rhythm disturbances, without any alternative form of treatment available and with a poor prognosis.
In daily practice this means patients with severe, symptomatic, end stage heart failure (NYHA IIIB-IV) despite (evidence based) optimal medical and device therapy apparent from:

- Maximum tolerated doses Renin Angiotensin Aldosteron System Inhibition, Beta-Blockers and Mineralocorticoid Receptor Antagonists (MRA)
- CRT-P/D has been considered and/or implanted according to guidelines
- Revascularisation, rehabilitation and other interventions to improve cardiac status and quality of life of patients have been considered and/or performed

- VO2max ≤ 12 ml/kg/min on Beta-blocker, ≤ 14 ml/kg/min in patients not on beta-blocker, or VO2max < 50% of predicted VO2, in younger patients and women

A strong motivation and request of patient to receive heart transplantation is mandatory.

The selection of patients is based on three items which have to be combined, and taken into context with the rest of the data.

These diagnostic items are: *cardiopulmonary stress testing*, *prognostic stratification* and *diagnostic right-heart catheterization [2]*.

Cardiopulmonary stress testing
A maximal cardiopulmonary exercise test is defined as achievement of an anaerobic threshold on optimal pharmacologic therapy with a RQ ≥ 1.05. In the presence of a Beta-blocker, a cutoff for peak VO2 ≤ 12 ml/min/kg should be used to guide listing. In patients intolerant for Beta-blocker, a cutoff ≤ 14 ml/min/kg should be used. Especially in younger patients and women, ≤ 50 % of predicted VO2 can be used as additional criteria. In obese patients, expressing peak VO2 as ml/min should be considered, to prevent false low numbers when using ml/min/kg.
Listing patients solely on the criterion of a peak VO2 measurement should not be performed [2].

Prognostic stratification
Assessment of prognosis is important in advanced heart failure to plan treatment and timely referral to a transplant center, but can be difficult in the individual patient. Risk markers and prognostic scores are extensively discussed elsewhere [11]. Heart failure survival scores may be used together with cardiopulmonary exercise testing to guide listing for heart transplantation for ambulatory patients.
A Seattle Heart Failure Model (SHFM) estimated 1-year survival of < 80% or a Heart Failure Survival Score (HFSS) in the high/medium risk range should be considered as reasonable cut points for listing. These scores are however not comprehensive and may overestimate survival in younger cardiomyopathy patients and they do not incorporate hemodynamic data and cardiopulmonary exercise results.
Listing patients solely on the criterion of heart failure survival prognostic scores should not be performed [11-15].

Diagnostic right-heart catheterization

Right-heart catheterization should be performed in all adult candidates in preparation for listing for heart transplantation and repeated annually (or more often in case of severe pulmonary hypertension) until transplantation. Often these diagnostic catheterizations are performed in the transplant center, after optimal medical therapy. The test is performed to assess the severity of heart failure, to support optimization of treatment and to determine the pulmonary vascular resistance (PVR). A higher PVR correlates with worse outcome after HTx [16,17].

A vasodilator challenge should be administered when the pulmonary artery systolic pressure is ≥ 50 mm Hg and either the transpulmonary gradient (TPG = PA mean - PCWP) is ≥15 mmHg or the PVR is > 3 Wood Units (> 240 dynes.sec.cm^{-5}), while maintaining a systolic arterial pressure > 85 mm Hg. Drugs used for this acute challenge are prostacyclin iv and nitroglycerin iv. Other drugs, like nitric oxide, diuretics, inotropes and vasoactive agents can be used in hospitalized patients to improve hemodynamics.

THE IMPLICATIONS OF CO-MORBIDITIES

Evaluation of comorbidities is important as they may negatively affect outcome after heart transplantation and thus have to be regarded as absolute or relative contra-indications.

Irreversible pulmonary hypertension / elevated pulmonary vascular resistance (PVR)

A severely increased risk of right heart failure and mortality after heart transplantation is thought to be present [2]:

- when the PVR is > 5 Wood Units (> 400 dynes.sec.cm^{-5}), or the PVRI is > 6 Wood Units.m^{2} (in children), or the TPG exceeds 16-20 mm Hg.
- if the systolic pulmonary artery pressure exceeds 60 mm Hg in conjunction with any 1 of the preceding 3 variables.
- If the PVR can be reduced to < 2.5 Wood Units with a vasodilator, only at the cost of a fall of arterial systolic blood pressure < 85 mm Hg.

LVAD's have been successfully used in patients with refractory elevations in PVR [18,19]. After LVAD implantation, hemodynamics should be re-evaluated after 3-6 months, before listing for heart transplantation.

Active systemic infection

An active systemic infection at the time of heart transplantation, when recipients are treated with high doses of immunosuppressive drugs, is still seen as an important contraindication, at least temporary.

Persistent infections, like HIV, Hepatitis B and C should be carefully analyzed on an individual basis.

-*HIV*: there are scarce data of organ transplantation and MCS in selected HIV patients. In these selected patients short-term survival was similar to that of the general heart transplantation population, but data on long-term outcome are lacking [20-24]. Also after LVAD implantation, short-term survival of selected HIV-patients was similar to that of the general LVAD population. Only highly selected candidates may be considered if they are clinically stable and compliant on antiretroviral therapy for a long time , have undetectable HIV-RNA and CD4 counts > 200 cells/ul and have no active or prior opportunistic infection. Patients with previous CNS lymphoma or visceral Kaposi sarcoma should not be considered [2].

The decision to accept potential candidates for heart transplantation with complex comorbidities should always include the increasing shortage of donor hearts in general. Furthermore, one has to realize that the management of antiretroviral therapy in combination with immunosuppressive therapy is very challenging due to substantial pharmacological interactions [22,25] and often will restrain transplantation as a feasible solution.

-*Hepatitis B*: patients with resolved hepatitis B infection may be considered candidates for HTx, but require full serological and viral load testing at screening and every 3 months while listed and at the time of transplantation. In patients with chronic hepatitis B infection, liver biopsy should be performed in all patients to exclude severe disease. Cirrhosis, portal hypertension or hepatocellular carcinoma are contraindications to HTx. Clearly, acute hepatitis B is also a contraindication [2].
-*Hepatitis C*: patients with resolved or prior inactive hepatitis C infection may be considered candidates for HTx, but require full serological and viral load testing at screening and every 3 months while listed and at the time of transplantation. In patients with chronic hepatitis C infection, HCV genotype and a liver biopsy is required. Cirrhosis, portal hypertension or hepatocellular carcinoma are contraindications to HTx [2].

Extensive analysis of hepatitis B and hepatitis C candidates by an experienced hepatologist is always indicated.

Active malignancy or history of malignancy with probability of recurrence
Active neoplasm from origins other than the superficial skin (basal cell carcinoma and squamous cell carcinoma) is an absolute contraindication to heart transplantation due to the limited survival rates [2]. However, patients with a history of malignancy can be considered for heart transplantation when the risk of tumor recurrence is low, preferable after a reasonable time of complete remission (at least 5 years), depending on tumor type, response to therapy and negative metastatic work-up. Collaboration with oncology specialists is mandatory in all patients. LVAD's can be used in these patients as a bridge to candidacy.

Inability to comply with complex medical regimen
Compliance, the capacity to adhere to a complex lifelong regime of drug therapy, lifestyle changes and regular follow-up, is a crucial element in attaining long-term success after transplantation[2]. This includes the adequate use of all medication, because suboptimal use of immunosuppressive medication plays a major role in most acute rejections occurring more than 6 months after transplantation and it is also related to subsequent cardiac allograft vasculopathy (chronic rejection) [26] which is a major cause of mortality late after HTx.
Also substance abuse (alcohol, drugs) and tobacco use have to be taken into consideration as it is thought that especially substance abuse is an important predictor of non-compliance [27]. Tobacco use continues to be the foremost avoidable cause of death in the western world with an enormous impact on cardiovascular diseases and malignancies. Small studies have demonstrated increased incidence of coronary allograft vasculopathy and malignancy, along with decreased survival in those patients who return to smoking after transplantation [28]. Active tobacco smoking during the previous 6 months is a risk factor for poor outcomes after transplantation and therefore considered a relative contraindication[2].
To evaluate the patient's ability to comply with instruction including drug therapy, a psychosocial assessment should be performed before listing for transplantation.

Severe peripheral or cerebrovascular disease
Severe peripheral or cerebrovascular disease may contribute to both poor prognosis for survival as well as poor quality of life on a noncardiac basis and therefore should be considered as a major comorbidity that can preclude eligibility for heart transplantation [29].

The severity of symptoms and the potential options for revascularization may affect this decision, although it is not clear whether post-transplant risk can indeed be modified by revascularization.

Irreversible severe dysfunction of another organ
All co-morbidities which adversely impact prognosis after transplantation should be weighed individually.

Age has to be seen as a continuous risk factor for outcome after heart transplantation [3]. The increased risk of older age is not so much caused by the age itself, but more by the biological age, especially in combination with frailty, cachexia and sarcopenia.
Frailty includes symptoms like unintentional weight loss ≥ 5 kg within the past year, muscle loss, fatigue, slow walking speed and low levels of physical activity [30,31].

Chronic kidney disease is a very important risk factor for mortality post transplantation. Irreversible renal dysfunction with a GFR < 30 ml/min/1.73 m^2, as estimated by the creatinine clearance or eGFR, should be considered as an absolute contraindication for heart transplantation alone [2]. In general, renal function will further deteriorate after heart transplantation, mainly as a result of the nephrotoxic immunosuppressive drugs. Many patients after heart transplantation end up on dialysis or even secondary kidney transplantation.
Although combined transplantation of a heart and a kidney from the same donor is technically feasible it should only be rarely considered in the most appropriate individuals to maximize the supply of limited organs [2].

Diabetes mellitus with signs of end-organ damage (other than non-proliferative retinopathy alone) or persistent poor glycemic control is a relative contraindication for transplantation [2,32].

Obesity. Patients with a BMI > 35kg/m^2 have longer waiting times, are less likely to get a suitable donorheart and show a higher post-transplant morbidity and mortality. Therefore it is reasonable to strongly recommend weight loss to achieve a BMI < 35 kg/m^2, and preferably < 32 kg/m^2 before listing for cardiac transplantation [2,33-35].

Cardiac amyloidosis is a rare disease characterized by the infiltration of misfolded proteins in several organs, like heart, kidneys and peripheral nerves. Several types are known of which AL-amyloidosis and TTR-amyloidosis may localize in the heart. Evaluation and treatment should be restricted to experienced centers. AL-amyloidosis is essentially a malignant hematologic disease which should be treated by chemotherapy and preferably stem cell transplantation. TTR-amyloidosis can be familial due to a mutation, or as a result of older age (wild-type or senile). As the TTR protein is primarily produced in the liver, in mutant TTR-amyloidosis, liver transplantation or combined liver and heart transplantation has been performed in very selected patients. The results of liver transplantation alone are disappointing because of ongoing wt TTR deposition in the heart after liver transplantation. Combined liver and heart transplantation do show better survival results but the numbers are low and real long-term follow-up is lacking [36,37]. Recently, heart transplantation-only has also shown good outcome in very selected patients [38].
In wild type TTR-amyloidosis, in general older age precludes heart transplantation.
Several new drugs for the treatment of TTR-amyloidosis, like tafamidis and patisiran recently became available, which will certainly impact future treatment [39].

DECISION MAKING

As stated above, the indications and contraindications for heart transplantation as well as the guidelines for the acceptance of donor hearts are broadly defined. The final acceptance is done by the heart transplant team which has extensive knowledge of the treatment of patients with advanced heart failure on the one hand and thorough experience with heart transplantation and mechanical circulatory support on the other hand. Heart transplantation is a very limited and complex treatment modality for only a few patients. It requires a dedicated team of specialists, consisting of at least cardiologists trained in advanced heart failure, heart transplantation and mechanical circulatory support, as well as infectious diseases and immunology, cardio-thoracic surgeons with extensive experience in surgical therapies of advanced heart failure, anesthesiologists with cardiac experience, and specialized nurses and psychologists/social workers.
To emphasize again, in contrast to other complex medical therapies, heart transplantation is a form of therapy with very limited "resources" and therefore requires extensive judgment to make the most optimal use of this modality.
That is why it is also important that outpatients on the waiting list for heart transplantation should be regularly re-evaluated (at least every 6 months) preferably with cardio-pulmonary exercise testing and heart failure prognosis scores. If they have improved significantly, they should be considered for delisting [2].

In case a patient or his/her referring physician does not agree with the decision made by the transplant team of one center, a second opinion in one of the other centers should be possible.

REFERRAL

All heart failure patients should undergo regular follow-up to detect progression of symptoms and disease and estimate their long-term prognosis. Timely referral to a tertiary center for advanced heart failure, to consider advanced therapies like heart transplantation and mechanical circulatory support is essential [11]. Markers of advanced heart failure which may help in this referral include: requirement of iv inotropes, persisting class III to IV NYHA, progressive renal failure, LVEF < 20%, recurrent ICD shocks, more than 1 hospitalization in the previous year, persisting fluid overload or increasing diuretic requirement, low blood pressure, inability to tolerate ACE-I, ARB, ARNI or beta-blockers.
Referral of a patient to a transplant center should be accompanied by sending extensive written information including a summary of the complete medical history and current data, including:

- Cardiac and non-cardiac history
- Chest X-ray
- Laboratory examination
- Surgery report in case of prior cardiac surgery
- Heart catheterization data
- Cardiac imaging, including echocardiogram and MRI
- Exercise test when available
- Psychological/social information, when available

ALLOCATION OF DONOR ORGANS

According to the Dutch law on organ donation, all organs are allocated centrally, using patient-oriented allocation according to pre-specified requirements by the centers. Responsible for this is the "Nederlandse Transplantatie Stichting", (NTS) which has outsourced the specific allocation to Eurotransplant (ET). Organs are allocated according to blood group, body size, medical urgency and waiting time. Final acceptance of a donor heart is the responsibility of the transplantation team, which will weigh all the donor data in combination with the actual situation of the potential recipient. For heart donation, the upper age limit is ± 65 years. The only absolute specific cardiac contra-indication for heart donation is the presence of significant heart disease, like angina pectoris, myocardial infarction, prior coronary bypass surgery, moderate to severe valvular disease, cardiomyopathy or important arrhythmias. General contra-indications for all donations are for example, untreated sepsis, malignancies and infections without adequate treatment.
In the work-up of a potential heart donor, the medical history, an electrocardiogram and a Trans-Thoracic Echocardiogram (TTE) are essential, besides hemodynamic data and markers for cardiac damage, including troponin. In case the left ventricular function cannot be reliably evaluated by TTE, because of insufficient acoustic window in a ventilated patient, Trans Esophageal Echocardiography (TEE) is mandatory. In hemodynamically unstable patients, a Swan-Ganz catheter should be used to optimize the filling status of the patient. Given the generally higher donor age in the Netherlands, coronary angiography is advised to rule out significant coronary artery disease in older donors (i.e. > 50 Years) or other patients with risk factors for coronary artery disease.
With respect to the low number of donor hearts in the Netherlands, two important initiatives have to be mentioned which hopefully will lead to an increase of useable hearts. The first is the new law on organ donation which includes active donor registration which recently has become operational. The second is the introduction in the Netherlands of the use of donor hearts after circulatory determined death (DCD). Presently, only hearts from donors following brain stem death are used for transplantation (DBD). About half of all organ donations in the Netherlands are DCD procedures of which the kidneys, liver and lungs are used for transplantation. Recent developments in organ perfusion and retrieval techniques will also safely allow the use of hearts from these donors, as was demonstrated by several centers in the UK and resulted in a substantial increase in the number of donor hearts [40].

MECHANICAL CIRCULATORY SUPPORT AND HEART TRANSPLANTATION

As mentioned in the introduction, due to the shortage of donor hearts and the progressively increasing waiting time, more and more patients are being treated by a LVAD as bridge to transplantation. Indications and contraindications for LVAD therapy can be found in the "Consensus Document LVAD therapie van de Werkgroep Mechanical Circulatory Support NVT-NVVC".
Already 50-70% of the patients being transplanted were implanted with a LVAD first and the expectation is that this number will grow even further. If the number of donor hearts will not increase substantially, given the promising short and medium long-term outcome of the present LVAD's, the surgical treatment of advanced heart failure will change considerably in the coming years [5].
Only patients with primarily right sided heart failure, complex congenital heart disease or hypertrophic cardiomyopathy, may undergo primary heart transplantation. All other patients will undergo long-term mechanical circulatory support first and only in case of complications not amenable by LVAD replacement, heart transplantation will be considered. A growing number of patients who are implanted with a LVAD as bridge to transplantation do already prefer not to be placed directly on the waiting list for heart transplantation [6,9]. On the other hand, patients with advanced heart failure treated by an LVAD as alternative for heart transplantation (so called "destination therapy") may in time qualify for heart transplantation in case of improvement of

relative contra-indications like pulmonary hypertension, renal failure and curation of malignancy (bridge to decision). So, heart transplantation and MCS are deeply interwoven therapies and should be considered side by side in the treatment options for patients with advanced heart failure.

SUMMARY AND CONCLUSION

Heart transplantation is yet considered to be the gold standard therapy for refractory heart failure in carefully selected patients with a high likelihood of improvement after the transplantation. Timely referral to a transplant center should be considered in those patients demonstrating markers of advanced heart failure like the requirement of iv inotropes, persisting class III or IV NYHA, progressive renal failure, severe LV or RV dysfunction, recurrent ICD shocks, more than 1 hospitalization in the previous year, persisting fluid overload or increasing diuretic requirement, progressive cardio-renal syndrome and the inability to tolerate evidence based therapy. Given the scarcity of donor hearts, careful selection of the most suitable candidates is mandatory. The growing discrepancy between potential recipients and the availability of donor hearts, results in a growing number of patients who need a LVAD first, as bridge to transplantation. New initiatives, including active donor registration and DCD heart donation will hopefully have a positive effect on the availability of donor hearts in the Netherlands.

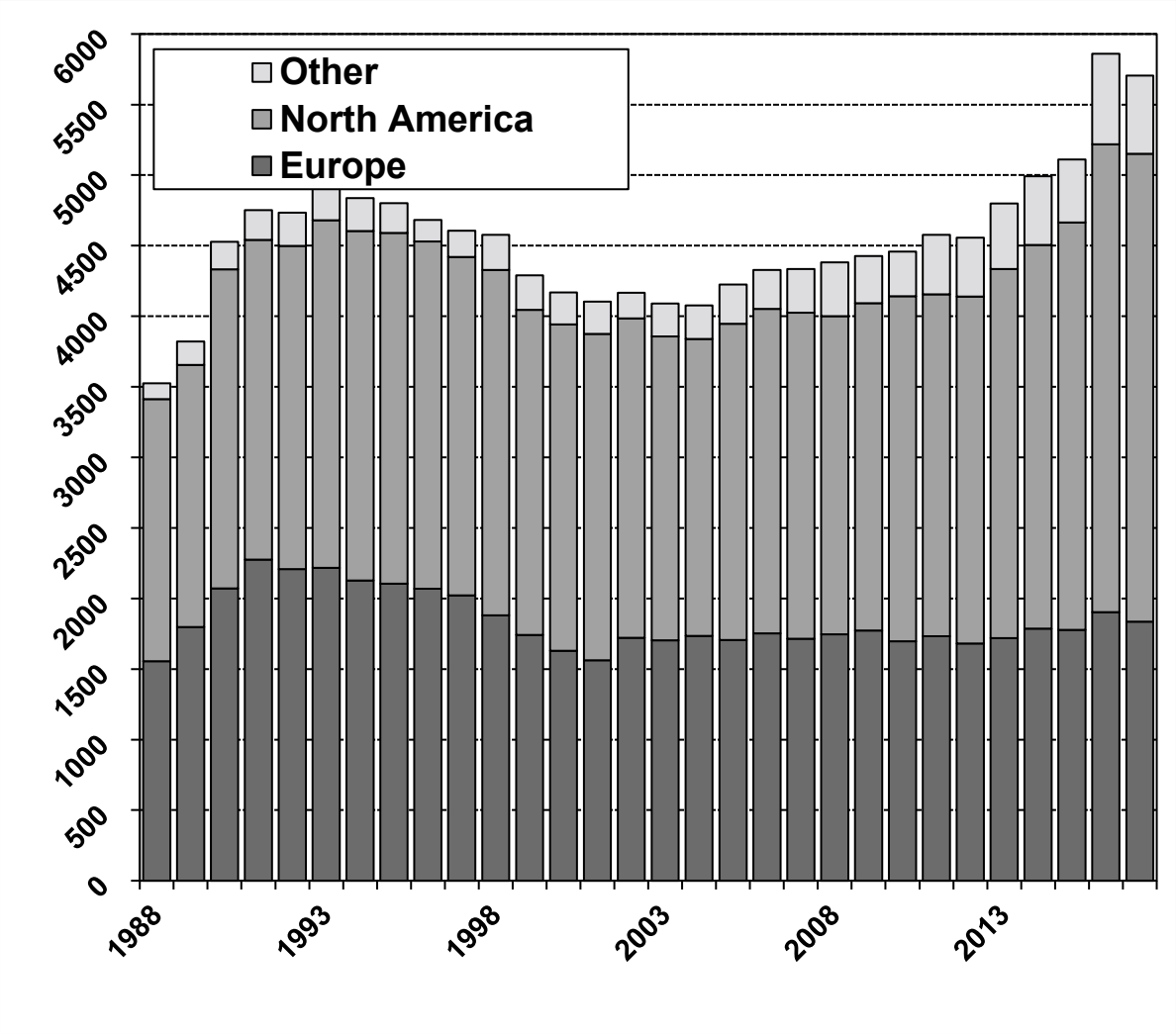

Fig 1a: the number of heart transplantations per year according to the International Society for Heart and Lung Transplantation [3]

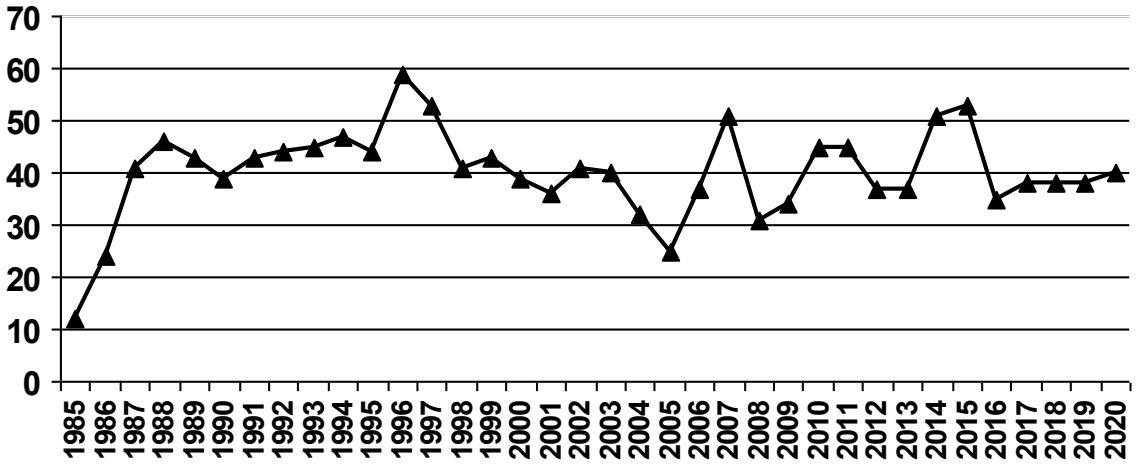

Fig 1b: the number of heart transplantations per year in the Netherlands

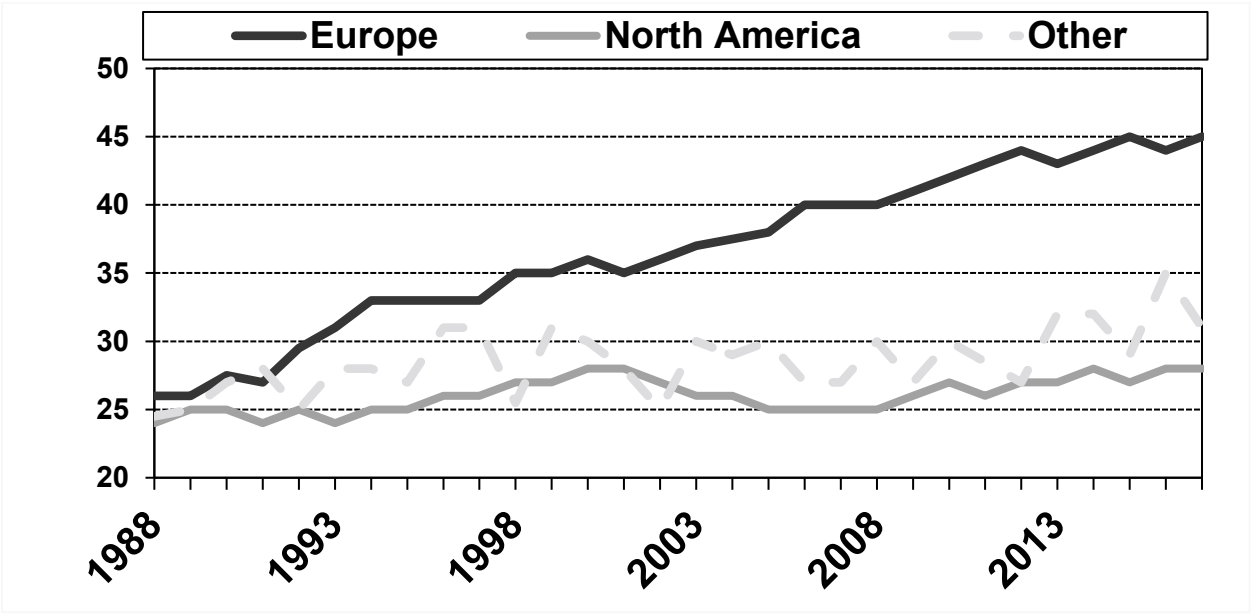

Fig 2 Median donor age by location according to the International Society for Heart and Lung Transplantation [3]

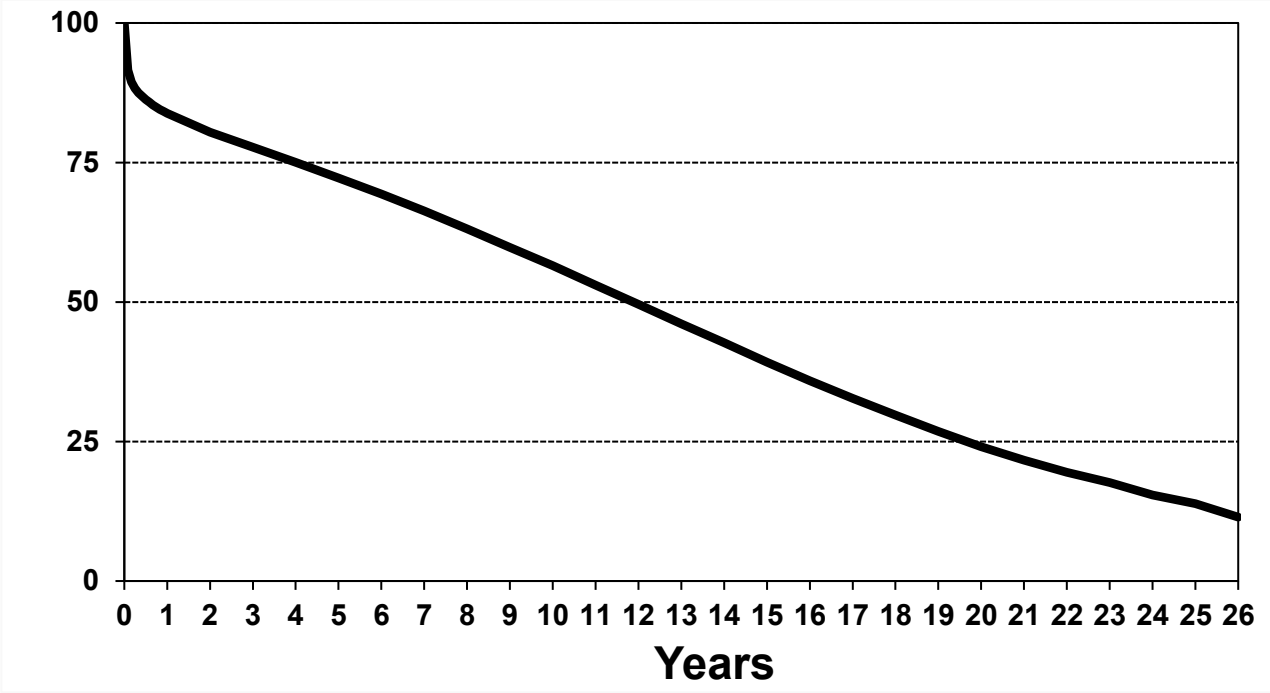

Fig 3: Survival (%) after heart transplantation according to the International Society for Heart and Lung Transplantation [3]

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